REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1-21, 23-25 and 27-38 are pending. The amendments are fully supported by the original disclosure and, thus, no new matter is added by their entry. For example, amendment of claim 6 is based on page 4, lines 28-29; page 6, lines 32-33; and page 7, lines 8-9 and 23-24, of the specification. New claims 29 and 35 are combinations of limitations recited in original claims 1-2 and 4. Additionally, claim 29 requires integration of at least one DNA into the modified host cell's genome (page 5, line 27; page 11, line 20; and page 12, line 12, of the specification) and claim 35 requires dilution and loss of the DNA's fluorescent label in progeny of the transfected host cells (page 6, line 9; page 11, line 21; page 12, lines 13-14; and page 13, lines 17-18, of the specification).

Claims 1-9 were examined on the merits. Claims 10-21, 23-25 and 27-28 were withdrawn from consideration by the Examiner as directed to non-elected inventions. Applicant maintains that claims 1-9, 15 and 27-39 are drawn to the elected invention. Therefore, a petition against the restriction requirement is being submitted herewith because claims 15 and 27-28 should have been examined in this application instead of being withdrawn from consideration.

Non-elected claims 10-14, 16-21 and 23-25 were also withdrawn from consideration by the Examiner. These withdrawn claims should be examined in this application upon allowance of the elected claims because the elected invention and the non-elected inventions are related as combination-subcombination.

Claim Objections

Claims 1 and 8 were objected to as allegedly informal. They are amended to correct the informalities as suggested by the Examiner.

Withdrawal of the objection is requested.

35 U.S.C. 112 – Written Description

The specification must convey with reasonable clarity to persons skilled in the art that applicant was in possession of the claimed invention as of the filing date sought.

See *Vas-Cath v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). But the Patent Office has the initial burden of presenting evidence or a reason why persons of ordinary skill in the art would not have recognized such a description of the claimed invention in the original disclosure. See *In re Gosteli*, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989).

Claims 1-9 were rejected under Section 112, first paragraph, because they allegedly contain "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Applicant traverses.

The specification teaches a representative number of species within the claimed genus. In particular, it was alleged that the genus of host cells, polynucleotides, labels, and metabolic properties are not adequately described in Applicant's specification. Multiple species within each genus are well known to the skilled artisan. Host cells may be prokaryotic cells (e.g., bacteria) or eukaryotic cells (e.g., yeasts, fungi, plant cells, animal cells) (see page 6, lines 10-11, of the specification). Examples of polynucleotides are DNA, RNA, short hairpin RNA, non-coding RNA, LNA, HNA, and PNA (see page 4, line 32, et seq. of the specification). The label may be fluorescent label, luminescent label, chemoluminescent label, enzymatic label, magnetic label, antigenic label, or a radioactive label (see page 5, lines 29-31, of the specification). Finally, examples of metabolic properties are well known in the art (e.g., improved metabolite production, altered morphology or growth on a specific substrate). More specifically, the metabolic property may be producing a RNA by transcription, a recombinant protein such as antibody or enzyme by translation), a primary or secondary metabolite, or biomass such as yeast cells (see page 5, lines 3-7, of the specification). The primary metabolite may be an amino acid, steroid, or nucleotide; the secondary metabolite may be an antibiotic, vitamin, anti-infective, macrolide, polyketide, pheromone, alkaloid, or other drug (see page 7, lines 15-18, of the specification).

The discussion of *Univ. of Rochester v. G.D. Searle & Co.* on pages 7-8 of the Office Action failed to acknowledge that the Court's holding of lack of written description was based on completely different facts. In *Rochester*, the claimed method used a non-steroidal compound that was never described by a specific example or chemical struc-

ture. The only requirement was for the compound to selectively inhibit PGHS-2 activity. The inventors of the '850 patent did not possess the claimed method because they did not identify any compound that would have satisfied the limitations of their claim ("No compounds that will perform the claimed method are disclosed, nor has any evidence been shown that such a compound was known"). Here, by contrast, Applicant has actually reduced his invention to practice. The Examiner has not identified any specific technical problem associated with using host cells, polynucleotides, labels, or metabolic properties other than those that were illustrated as non-limiting examples by Applicant.

Therefore, the present specification conveys to the skilled artisan that Applicant had possession of the claimed invention. Withdrawal of the written description rejection is requested.

35 U.S.C. 112 – Enablement

The Patent Office has the initial burden to question the enablement provided for the claimed invention. M.P.E.P. § 2164.04, and the cases cited therein. It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *In re Marzocchi*, 169 USPQ 367, 370 (C.C.P.A. 1971). Specific technical reasons are always required. See M.P.E.P. § 2164.04.

Claims 1-9 were rejected under Section 112, first paragraph, because allegedly "[t]he specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims." Applicant traverses.

No specific technical reasons are provided by the Examiner that would prevent a skilled artisan from practicing the claimed invention. For example, she alleged, "No correlation is made between the structure of the DNA and its function in the method." But Applicant's invention does not require the use of any specific DNA structure. The polynucleotide is labeled, which provides a non-inheritable trait to the transfected host cell, and permanently changes a metabolic property of the host cell after transfection.

Labels other than fluorescein and detection by techniques other than FACS (see pages 5-6 of the specification) could be used by the skilled artisan. Examples of metabolic properties are well known in the art (e.g., improved metabolite production, altered morphology or growth on a specific substrate). More specifically, the metabolic property may be producing a RNA by transcription of DNA, a recombinant protein such as antibody or enzyme by translation of RNA, a primary or secondary metabolite, or biomass such as yeast cells (see page 5, lines 3-7, of the specification). The primary metabolite may be an amino acid, a steroid, or a nucleotide; the secondary metabolite may be an antibiotic, a vitamin, an anti-infective, a macrolide, a polyketide, a pheromone, an alkaloid, or other drug (see page 7, lines 15-18, of the specification). The biochemical pathways for their metabolism and the enzymes involved in their synthesis are well known.

The Examiner does not provide evidence or acceptable reasoning for limiting the claimed invention to pGBDEL4L, fluorescein label, and FACS detection. Surely other polynucleotides known in the art to permanently change a metabolic property could be used such as those encoding an antibody or enzyme, antisense, and RNAi. They could be labeled by other fluorescent or non-fluorescent labels, and such labels are known in the art because they can be detected directly or indirectly through a variety of detection techniques using well-known chemical and physical principles.

Therefore, the present specification enables the skilled artisan to make Applicant's claimed invention without requiring undue experimentation. Withdrawal of the enablement rejection is requested.

35 U.S.C. 102 – Novelty

A claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is claimed. See *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Claims 1-4 and 6-9 were rejected under Section 102(b) as allegedly anticipated by Wolff et al. (U.S. Patent 6,262,252). Applicant traverses.

Independent claim 1 (and all claims depending from claim 1) is not anticipated by Wolff. Gene transfer as required by Applicant's claim 1 requires (i) transfecting a polynucleotide, which is labeled with a non-inheritable trait, into a host cell and (ii) permanently changing metabolism of the host cell due to the transfected polynucleotide. Applicant does not agree with the Examiner's allegation that Wolff discloses gene transfer as required by the present claims. The permanent change in a metabolic property requires stable transfection of the host cell by the polynucleotide. But the '252 patent does not teach or suggest evidence of a permanent change in a metabolic property in the transfected host cells. Additionally, the isolation of transfected host cells was not disclosed by Wolff since, at most, transfected host cells were detected by fluorescent microscopy. There was no isolation of the transfected host cells, or separation of transfected from non-transfected cells. The Examiner refers to paragraphs 95, 105 and 107 but the paragraphs of the '252 patent are not numbered. On page 8 of Applicant's prior response, the Examiner was requested to cite to the column and line numbers of the '252 patent but she did not do so in the pending Office Action. What columns and lines correspond to her paragraphs 95, 105 and 107?

The Examiner did not find Danko, a document submitted by Applicant in the last response, as relevant because that document does not refer to the disclosure of Wolff. This is not a requirement for relevant evidence. Here, Danko is relevant to this rejection because Wolff is an inventor of the '252 patent and an author of Danko et al. (Hum. Mol. Genet. 6:1435-1443, 1997). In fact, Danko could not have referred to the cited patent since the former was accepted for publication on June 23, 1997 and the '252 patent was not filed until December 2, 1997. Nonetheless, Danko is relevant to whether pCIluc is able to permanently change a metabolic property of transfected host cells under the conditions employed in the prior art. Column 18, lines 36-38, of the '252 patent clearly teaches that Danko's pCIluc is the same as the plasmid DNA used in the cited patent. This nexus demonstrates the cited document's relevance. Thus, Danko's teaching that transfection of host cells using pCIluc had only temporary effects on gene expression shows that permanent change in a metabolic property is not necessarily inherent in the method disclosed in the '252 patent.

Transient transfection as shown in the prior art is different from the stable transfection required to permanently change a metabolic property. This difference is known in the art. Danko discloses transient transfection, which does not permanently change a metabolic property of the host cell. Example 11 of the '252 patent also fails to disclose stable transfection or a permanent change in a metabolic property of the host cell. If this rejection is maintained, the Examiner is respectfully requested to state what metabolic property is permanently changed as a result of Wolff's method. Further, since Wolff's cells were fixed and analyzed by fluorescence microscopy only one hour after pCIluc transfection, it is unlikely that there was any cell proliferation during subsequent culture as required by Applicant's claim 6.

On pages 13-14 of the Office Action, the Examiner referred to Applicant's paragraph [0045] (Example 4) and paragraph [0047] (Example 5). Note that the passages quoted by her are actually stitched together from two different examples. The Examiner alleged that because Applicant used a fluorescein-labeled polynucleotide and Wolff also used a fluorescein-labeled plasmid, Wolff's cell is inherently modified. But Wolff did not follow the protocol described in either Applicant's Example 4 or Example 5. Both of those examples, as well as Applicant's claim 1, require isolation of the transfected host cell after the polynucleotide is transfected. In the quoted passage, Applicant's sorting of fluorescent cells from non-fluorescent cells resulted in isolation of the transfected host cells. This requirement in Applicant's claim 1 for isolation of the transfected host cells is lacking in Wolff. Therefore, Wolff's method does not necessarily result in a modified host cell that is permanently changed in a metabolic property and Wolff's cell is not inherently modified as required by Applicant's claimed invention.

Claims 1-9 were rejected under Section 102(b) as allegedly anticipated by Johnson et al. (AAPS Pharmsci 1:article 6, 1999). Applicant traverses.

Independent claim 1 (and all claims depending from claim 1) is not anticipated by Johnson. Gene transfer as required by Applicant's claim 1 requires (i) transfecting a polynucleotide, which is labeled with a non-inheritable trait, into a host cell and (ii) permanently changing metabolism of the host cell due to the transfected polynucleotide. Applicant does not agree with the allegation that Johnson discloses gene transfer as

required by the present claims. The perinuclear staining (i.e., fluorescence detected around or surrounding the perimeter of the nucleus) is not indicative of the entry of polynucleotide into the host cell's nucleus (i.e., integration) where it would be required for a permanent change in a metabolic property (e.g., stable gene expression). On page 6 of Johnson, the detection of cells that had internalized DNA as early as 1 hr after transfection was contrasted with the 24 to 48 hr that is typically required for the measurement of the expression of a reported gene. The permanent change in a metabolic property (e.g., stable expression of a heterologous gene in the polynucleotide) requires stable transfection of the host cell by the polynucleotide. No permanent change in cell growth was observed after transfection. Johnson also admits on page 6, "Because the present study was not designed to examine the cytoplasm-to-nucleus transfer of exogenous DNA, we did not examine the intracellular location of the transfected DNA." Although the cited document fails to disclose this limitation of Applicant's claim 1, Johnson suggests that the transfected DNA is located in the nucleus although this was admitted in the preceding portion of the paragraph to be an issue left unexamined. The "early events of DNA transfection" (abstract) examined by Johnson would occur before the integration of polynucleotide and without a permanent change in a metabolic property.

The portion of Johnson quoted by the Examiner on page 14 of the Office Action discusses internalization of DNA into the cell (i.e., intracellular DNA). Johnson does not disclose that the DNA was internalized into the nucleus ("the present study was not designed to examine the cytoplasm-to-nucleus transfer of exogenous DNA"). Transient transfection as shown in the prior art is different from the stable transfection required to permanently change a metabolic property. This difference is known in the art. Johnson discloses transient transfection that does not permanently change a metabolic property of the host cell. The cited document uses pGL3-control plasmid for transfection, but there is no evidence that a transected cell permanently expresses lucferase. If this rejection is maintained, the Examiner is respectfully requested to state what metabolic property is permanently changed as a result of Johnson's method.

Withdrawal of the Section 102 rejections is requested because the cited documents fail to disclose all limitations of the claimed invention.

Conclusion

Having fully responded to the pending Office Action, Applicant submits that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if additional information is required.

Respectfully submitted,

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